immunogens administered are selected from the group consisting of BCG, diphtheria, tetanus, pertussis,[1] polio, hepatitis B, hemophilus influenza, measles, mumps and rubella immunogens. Old conditions (a)-(c) are replaced by two new conditions. If all of the immunogens are from the aforementioned group, then at least one of new conditions (a) and (b) must be met. Condition (a) is that immunogens are administered on at least three different dates prior to 42 days after birth. These dosings may be with the same or different antigens. For example, one could give pertussis at 7, 21, and 35 days of age, or pertussis and 7 and 21 days of age, and measles at 14 days of age. Condition (b) is that immunogens are administered on at least three different dates (not necessarily all prior to 42 days after birth) and the maximum interval between administrations is about two weeks, or less.

New claim 58 parallels but does not refer to immunization against an infectious disease. Claim 59 parallels claim 18, but is dependent on 58.

Claims 21-34 and 37 have been amended to require that

(1) the mammal is a human, or an animal model of a human diabetes (and streptozocin-treated mice are expressly excluded), and

(2) the mammal receives at least one of the following immunogens prior to an age of 24 months: hepatitis B, hemophilus influenza B, mumps, rubella, chicken pox, acellular pertussis, and pneumococcus immunogens.

The significance of the second limitation is that the recited immunogens (all of which appear in the specification, see original claim 18, and page 55, line 7) did not come into clinical use until after the publication date of the references cited as showing inherent anticipation, and hence this limitation

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[1] Claim 3 now refers to "whole cell" pertussis in this proviso.

prevents inherent anticipation, since the authors of the references would have identified any experimental immunogens used.

Claim 27, 35 and 38 have been cancelled.

Claim 41 has been rewritten in independent form. New claims 42-46 and 49 are dependent on claim 41.

New claims 47 and 48 are dependent on claim 3.

Claim 50 is a new independent claim. It has the same two new limitations that were added to amended claims 21-35 and 37. New claim 51-56 are dependent on claim 50. New claim 57 relates to immunization with conjugated pneumococcal or varicella vaccines, as well as with at least one of certain specified immunogens.

Response to Rejections

1. The Examiner has rejected several claims as inherently anticipated by various references, as tabulated below:

Ref	Claims	Comments
Lee et al.	2, 3, 6-14, 16, 33	pertussis at 7 and 21d to piglets, or 6 and 12d to mice
Barrett et al.	2, 3, 6-9, 11-14, 16-17, 21, 22, 25	DPT 4x, 4 wks apart, beginning at 24-48 h
Halsey et al.	21	DPT at 1, 5 and 9 wks
Provenzano	3, 6-9, 11-14, 16, 17, 25, 28-31, 33, 34	DPT at 0, 3, 6, 10 and 14 wks
	24	DPT at 10 and 14w, P at 3 and 6 w.

In each of these rejections, the Examiner concedes that the

effect of the protocol on the incidence of diabetes was not tested in the reference, and tacitly acknowledges that the reference does not suggest that the protocol would reduce the incidence of diabetes. Rather, she argues, based on applicants' disclosure, that the methods disclosed in the reference would inherently produce the claimed effect. This rejection is respectfully traversed.

Lee's subjects were not humans, or animal models of a human autoimmune disease, so Lee does not inherently anticipate the present claims.

Barrett, Halsey and Provenzano describe immunization protocols in which the third administration occurred when the subject was 42 days (6 weeks) old, or older (12 weeks old for Barrett, 9 weeks old for Halsey, and 6 weeks old for Provenzano). Hence, they do not inherently anticipate condition (a) of the proviso of amended claim 3. They do not satisfy condition (b) either, as the maximum interval between administrations was three weeks for Provenzano and four weeks for Barrett.

Nor do they inherently anticipate claims 21-34 and 37. These claims all require administration of immunogens which did not come into clinical use until after the reference dates. For example, according to Zinsser Microbiology (Ex. A), the mumps vaccine was licensed in 1968 and the rubella vaccine in 1969.

2. In paragraphs 11-16 and 19 of the office action, various claims are rejected as obvious over Lee or Barrett, which the Examiner conceded did not teach use of an immunization protocol to reduce the incidence of diabetes, in view of various secondary references, as follows:

Para of OA	Claim	Secondary Ref
11	4, 5	Jegede et al. (CD)
12	10	none
13	18	Jagende et al.
14	23, 26	Madore et al.

15	27	Madore et al. Cohen et al.
16	30-32	Schaller et al. (B) Van Leengoed et al. (C)

Similarly, in paragraph 19, claim 37 is rejected as obvious over Halsey et al. in view of Satoh et al.

These rejections are respectfully traversed. First of all, the Examiner has not established a prima facie case of obviousness. As stated in MPEP §2142,

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP §2143-§2143.03 for decisions pertinent to each of these criteria.

Claims 2-14, 16-18, 21-35, and 37, as examined, were directed to methods of immunizing a mammal against at least one infectious disease while decreasing the incidence of diabetes mellitis or SLE. While Lee, Barrett and Halsey teach protocols

for immunization against an infectious disease, they do not suggest use of that protocol to reduce the incidence of diabetes or SLE.

Applicant has already explained how the amended claims avoid inherent anticipation by Lee, Barrett, and Halsey. Since Lee and Barrett and Halsey do not recognize that the choice of protocol affects the incidence of any autoimmune disease, they do not provide any motivation to alter their protocols in order to achieve reduced incidence of autoimmune disease. Nor do they provide any assurance that such reduction can be achieved with a reasonable expectation of success. In making a §103 rejection, the Examiner is not permitted to rely on Applicants' disclosure to establish that expectation, even though she could use it to argue inherent anticipation.

The secondary references do not remedy these deficiencies. Jegede et al. merely teaches use of an adenovirus immunogen to protect against diseases caused by that virus. Madore teaches administration of a hemophilus influenza immunogen at one month of life. Schaller et al. suggests that Mycoplasma hyopneumoniae antigens can be used to vaccinate swine. Van Leengoed discloses a vaccine for controlling Hemophilus pleuropneumonia in pigs. For all of these references the sole concern was protection against an infectious disease; the authors had no inkling that their protocol might affect the incidence of autoimmune disease.

The only secondary references to discuss the prevention of an autoimmune disease are Cohen, WO90/10449 and Satoh et al.

The Cohen patent application discloses the use of antigens which cross react with a 65kDa heat shock protein as a tolerizing agent. As discussed on pages 6-7 of our application, the problem with tolerogens of this type is that they are specific to the particular autoantigens with which they cross-react. They are not effective against autoimmune diseases mediated by other autoantigens.

The specification specifically states at page 18, line 27 to page 19, line 15:

> Tolerogens also are not generally considered immunogens in this invention, except as a tolerogen-immunogen, as described herein. A tolerogen is generally defined as an agent which induces a state of antigen specific immunological unresponsiveness to an antigen that immunologically cross reacts to the agent. Tolerogens are further considered agents that inactivate immune mediator cells like B and T lymphocytes by reacting to their antigen specific binding sight and inactivating the cells in an antigen specific manner. However, if a tolerogen has a component that is clearly immunogenic and causes activation of immune mediator cells resulting in antibody formation or T cell immune responses, then it can be both a tolerogen and an immunogen. A tolerogen-immunogen in the latter case may be employed in this invention to prevent chronic immune disorders by down regulating cells that do not directly bind to the tolerogen and/or prevent chronic immune responses against organs/antigens that do not cross react immunologically to said tolerogen.

It does not appear that Cohen's heat shock protein would be considered an "immunogen" within the meaning of the claim, as it is not capable of acting to elicit a specific immune response which protects against an infectious disease. Nonetheless, to facilitate prosecution, claim 48 has been added, which excludes the presence of Cohen's (and other) tolerogens.

3. Claims 28-34 are rejected as inherently obvious over Harris, et al., USP 4,152,415. Harris discloses administering a Treponema hyodysenteriae vaccine to swine. The vaccine is first administered parentally, e.g., on days 0 and 14, and is also given orally, on days 4-23, daily (See Experiment 1).

Harris does not inherently anticipate claims 28-34 because these claims now require either administration to either a human, or to a nonhuman animal which is an experimental model of an autoimmune disease. He does not render the claims obvious because there is no motivation to modify his protocol in order to reduce the incidence of autoimmune diseases in pigs, let alone in humans. Harris' sole concern is the prevention of swine dysentery. If a swine had an autoimmune disease, it would be culled, not treated.

4. Claim 35 is rejected as obvious over Ferreri et al (R) or (S) in view of General Recommendations on Immunization (AU).

Ferreri et al. (R) or (S) teach immunization of a human with hepatitis B vaccine at birth and at 15 and 45 days of age. The GRI are cited merely to indicate that immunization against HBV may be combined with immunization against other infectious diseases.

Claim 35 has been cancelled, so this rejection is moot. It is noted for the record that Ferreri does not inherently anticipate claim 3 because his third administration is after 42 days from birth, and his maximum interval is 30 days.

5. Claims 2, 3, 6, 7, 9-14, 16 and 33 are rejected as anticipated by Huang et al. (1984), which alleged discloses both immunization against pertussis by administering a pertussis immunogen at 45, 55, 59 and 85 days of life (see p. 221), and reduction in the incidence of diabetes.

Huang et al. (1984) cannot anticipate claims 2, 3, 6, 7, 9-14 and 16 because his first administration was to mice which were 45 days old, and claim 3 (the independent claim) requires a first

administration before 42 days from birth.

Nor does Huang et al. (1984) render obvious the use of an earlier (pre-42 days old) administration of pertussis immunogen in order to reduce the incidence of diabetes, in view of the ambivalent teaching by Kolb et al. (1987) and the negative teaching of Huang et al. (1991).

Kolb, et al (1987) also looked at the effects of a pertussis vaccine in a streptozotocin-treated mouse. The streptozotocin was administered when the mice were 8-11 weeks of age. The vaccine was given at day -3, +8, or +14 relative to STZ initiation. Given at day -3, it partially suppressed the hyperglycemia, while when given at days +8 and +14, it strongly enhanced it.

As admitted by Huang et al. (1991), "results from streptozotocin-induced IDDM experiments are difficult to extrapolate to type I IDDM because the correlation between chemically-induced diabetes and a "natural" development of autoimmune diabetes is unclear." Consequently, Huang et al (1991) examined the anti-diabetic effect of pertussigen in the genetically predisposed NOD mouse. These mice were give four injections of pertussigen at four week intervals, starting when the mice were 2 (Group 1) or 4 (Group 2 and 3) weeks of age. According to the authors, "although the time at which IDDM was first observed was delayed by several weeks, the incidence rates were not significantly different from those of untreated control NOD mice."

As for claim 33, it expressly excludes administration to streptozotocin-treated mice. Hence, Huang et al. (1984)'s mice could not anticipate claims 3 or 33.

6. Claims 3, 6-10, 14 and 16 are rejected as anticipated by, or obvious over, Huang et al. (1991).

Huang et al. (1991) immunized NOD mice at 2, 6, 10 and 14 weeks of age with pertussis immunogen. However, the authors

reported that the incidence of insulin-dependent diabetes in the immunized mice was not significantly different from that in the untreated control mice. If Huang's mice were accepted by the Examiner as a model of diabetes mellitis, then her inference of anticipation is rebutted by Huang's own findings.

Huang et al. (1991) would not inherently anticipate, even if an anti-diabetic effect were inherent. Claim 3, as amended, in condition (a), calls for three administrations of pertussis immunogen before 42 days after birth. Huang et al. (1991)'s third administration was at 10 weeks, i.e., 70 days, after birth. Condition (b) requires that the longest interval between administrations not exceed about two weeks. Huang's interval was four weeks.

Since Huang et al.'s finding was a negative one, it would have discouraged others from further experimentation with pertussis immunogen (such as variation of timing and/or dosage of immunogen) as an anti-diabetic agent, and hence cannot render the claimed invention obvious.

7. Claim 41 has been rejected as obvious over Ferreri, et al. (R) and (S), Lee et al., Barrett et al., Halsey et al., Huang, et al. (1991) or Harris et al. The deficiencies of these references has already been discussed, but we will briefly remind the examiner that only Huang et al. (1991) pertains to the use of an immunogen to prevent diabetes (as opposed to an infectious disease), and it concluded that the immunization was ineffective (thereby teaching away from the subject matter of claim 41).

The Examiner errs as a matter of law in dismissing the claim recitation of written instructions as being of "little weight". It would not have been obvious to label the kit as being for use in reducing the incidence of diabetes unless the references taught or suggested that the components of the kit were useful for that purpose.

In re Gulack, 217 USPQ 401, 403 (Fed. Cir. 1983) considered

the patentability of a claim to an educational or mathematical device with digits in a cyclical numerical series printed on an endless band. The Federal Circuit declared

> Differences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of the printed matter. Under section 103, the board cannot dissect a claim, excise the printed matter from it, and declare the remaining portion of the mutilated claim to be unpatentable. The claim must be read as a whole.

The Federal Circuit then went on to consider whether there was a functional relationship between the printed matter and the substrate, in view of the rule set forth by In re Miller, 164 USPQ 46, 48-9 (CCPA 1969). Finding that the band supported the digits, and that the cyclical numerical series exploited the endless nature of the band, the Federal Circuit found that the functional relationship was present. Finally, it held that the prior art neither disclosed nor suggested the claimed sequence of numbers.

Indefiniteness

Claim 33 was rejected as indefinite.

Antecedent basis for "separate" has been provided by amending at line 6 to insert --separate-- between "second" and "pharmaceutically acceptable dose".

The meaning of "during a 0-78 hour period" is clear from page 27, lines 25-28, page 52, lines 8-10. A single dose, rather than being delivered instantaneously, may be delivered over a prolonged period, up to 78 hours, and still be considered a single dose rather than multiple doses. Note that 78 hours is slightly (6 hours) under half a week, a week being 168 hours.

Improper Dependency

Claims 4 and 5 were rejected under §112, fourth para. as being of improper dependent form for failing to further limit the invention. This rejection is respectfully traversed.

According to Examiner

> The claims fail to further limit the subject matter of claim 3, since slaim 3 recites that all immunogens are selected from the group consisting of BCG, diphteria, tetanus, pertussis, polio, hepatitis B, hemophilus influenza, measles, mumps and rubella immunogens, while claims 4 and 5 recite that one immunogen other than the above listed immunogens (in addition to others) are administered.

The Examiner has misunderstood claim 3. This claim does not require that all of the immunogens be selected from the quoted Markush group. It says that if they are, then certain additional conditions (imposed to foreclose inherent anticipation) apply.

It should be noted, to clarify the record, that claim 18 also lists immunogens which are not listed in the Markush group of claim 3, but, for the reasons set forth above with respect to claims 4 and 5, complies with §112, fourth para.

Enablement

Claim 18 is rejected under §112, para. 1 as the disclosure is allegedly enabling only for claims limited to the listed immunogens other than a malaria or an HIV immunogen.

The present invention is directed to methods of reducing the incidence of an autoimmune disease, by early and frequent administration of immunogens.

It can be seen from both the experimental studies and the epidemiological data that a variety of immunogens -- plague,

anthrax, diphtheria, tetanus, pertussis, BCG, Hemophilus influenzae and smallpox -- can affect the development of diabetes, and that early administration of plague, anthrax, anthrax + pertussis, anthrax + DPT, and smallpox immunogens can reduce the incidence of diabetes.[2]

Table VI of the 1994 Declaration compared the anthrax, plague, DT, pertussis, Hib, BCG, smallpox and MMR vaccines in terms of the nature of the vaccine. There are considerable differences. Only the BCG vaccine has been shown to contain an immunogen that cross-reacts to an autoantigen associated with type I diabetes mellitus.

Under these circumstances, it is clear that the anti-diabetic response cannot be entirely immunogen-specific, as there is no common epitope in question which could be eliciting the response. A nonspecific immune response must play an important role.

At page 12, lines 7-25 of the specification, Dr. Classen declares

> Without intending to be bound by any theory, early administration of immunogens can cause the release of lymphokines that may accelerate the maturation of the immune system. The immunization may act in several ways including:
>
> A. Enhancing destruction of autoimmune prone cells in the thymus;
>
> B. Enhancing the flow of normal T-cells from the thymus;
>
> C. Causing peripheral elimination of autoreactive T-cells that have escaped the thymus;
>
> D. Causing the release of interferons which prevent infection with autoimmune causing viruses; and/or

---

[2] The effect of early administration of the other immunogens noted is not yet known, but is readily determined.

E. Causing migration of macrophages into the area of administration as in an injection site and away from an vital organ like the islet cells of the pancreas. The invading macrophages have the ability to act as antigen presenting cells and induce an autoimmune response against the vital tissue.

In contrast, the late administration of an immunogen can cause the release of lymphokines which may act as growth factors enabling autoimmune inducing cells to grown.

Lymphokines are discussed in more detail at pages 20-22 of the specification. Interferon alpha is specifically mentioned at page 21, line 19. The mechanism by which immunization with a broad range of vaccines at birth prevents diabetes can be explained through the release of alpha interferon (or other lymphokines). Alpha interferon is an molecule made by macrophages when they are activated by an immunological challenge such as an infectious organism or vaccine. Alpha interferon is routinely used to treat patients with hepatitis and other viral infections because the molecule has strong and broad antiviral activity. Alpha interferon induced by immunization at birth can help prevent diabetes through the suppression of congenital or neonatal infections, also called vertical infections. Studies from Sweden and Finland have indicated that 27% or more cases of insulin dependent diabetes are linked to a vertical infection with Coxsackie B virus. See Dahlquist, et al., Diabetologia, 38:1371-3 (1995); Hyoty, et al., Diabetes, 44:652-7 (1995). This data is consistent with early reports linking the development of insulin dependent diabetes to congenital rubella infections. Ginspberg-Gellner, et al., Diabetologia, 27:87-9 (1984). Inhibition of these infections through nonspecific mechanisms, in particular release of alpha interferon following immunization at birth, explains why early immunization is associated with a reduced risk for developing diabetes. This mechanism of action also explains why early immunization prevents diabetes in NOD mice since a congenital viral infection has been suggested as

a cause of diabetes in the NOD mouse. Gaskins, et al., J. Clin. Invest., 90:2220-7 (1992); Suenaga, et al., Diabetes, 37:1722-6 (1988); Nakagawa, et al., Diabetologia, 35:614-18 (1992).

The late administration of alpha interferon to patients has been reported to cause insulin dependent diabetes. Alpha interferon and the alpha interferon inducer Poly I:C have been shown to induce diabetes in rodents as well, explaining why late immunization induces diabetes in rodents. The induction of diabetes by late immunization also can be explained through the release of alpha interferon. The mechanism by which alpha interferon can induce diabetes include damaging the islet cells and speeding up a smoldering subclinical autoimmune disease.

The ability of interferon to modulate diabetes by two pathways, prevention through inhibiting viral infections and induction through stimulating an autoimmune response, explains the importance of timing of first immunization.

Potential immunogens, which could elicit, if administered early in life, an anti-diabetic immune response, are discussed in great detail at page 19, line 16 to page 20, line 17; page 24, line 11 to page 25, line 25; page 75, line 20 to page 76, line 2; page 77, lines 7-14; and original claims 18-20.

Methods of screening immunogens for suitability are discussed at length at pages 56-75, and are further exemplified by Examples 1 and 2 of the specification.

In view of the plethora of examples of potential immunogens, the diversity of the immunogens already known to affect diabetes, the plausibility of the proposed non-immunogen-specific mechanism (lymphokine release) by which the anti-diabetic effect is exerted, and the detailed presentation of the screening methodology, it is clear that one skilled in the art can, without undue experimentation, identify additional immunogens that can, by early administration, reduce the incidence of diabetes.

Therefore it does not appear that the disclosure is enabling

only for the listed immunogens, as other immunogens would be expected to have an anti-autoimmune disease effect and to be identifiable without undue experimentation.

With regard to malaria and HIV immunogens, in particular, the Examiner states that it would require undue experimentation to devise malaria or HIV immunogens which would protect against infection, since effective vaccines against these disease have not yet been produced.

There is no doubt that malaria and HIV immunogens have been identified in the art. Even if they have not yet been formulated into a vaccine effective against the infectious disease, that is no reason that their early administration will not elicit a nonspecific immune response which will reduce the incidence of an autoimmune disease.

It is true that claim 18, besides requiring reduction of the incidence of an autoimmune disease, also requires immunizing the recipient against at least one infectious disease. But nothing in claim 18 requires that the malaria immunogen itself be administered to prevent malaria, unless it is the only immunogen. If both pertussis and malaria immunogens were administered, the pertussis component would satisfy the requirement of immunization against at least one infectious disease, regardless of whether the malarial component was protective against malaria. In other words, the malarial component could be included merely for its value in reducing the incidence of the auto-immune disease. Similar comments apply to use of HIV immunogens.

The thrust of the present invention is not the development of methods of immunizing against infectious disease, but rather reducing the incidence of autoimmune diseases. If and when an effect anti-malaria or anti-HIV vaccine is developed, the present invention teaches <u>when</u> to administer it in order to decrease, not increase, the incidence of autoimmune diseases like diabetes. Applicants are entitled to coverage of not only immunogens

already known to be protective against infectious disease, but also those not yet proven as vaccines, or even associated with infectious diseases that have not yet become clinically important.

The claim includes a functional limitation: immunization against an infectious disease. If only a malaria or HIV immunogen is administered, and it is not protective, then the practiced method is, by definition, outside the claim. A functional limitation must be given weight in determining whether a claim is enabled. See Ex parte Mark, 12 USPQ2d 1904 (BPAI 1989) ("biological activity" required by claim).

New claim 59 parallels claim 18 but does not require immunization against an infectious disease. Applicants would consider deleting malaria and HIV from claim 18 if allowed to retain them in claim 59.

Respectfully submitted,

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Enclosure
-Exhibit A

Ex. A

EIGHTEENTH EDITION

Zinsser Microbiology

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APPLETON-CENTURY-CROFTS/Norwalk, Connecticut

Epidemiology

In susceptible populations, mumps virus infection is predominantly a disease of childhood, with the majority of clinically evident infections being seen between the ages of 5 and 10 years. It has been estimated that in the prevaccine era 90 percent of the population were immune by the time they reached 15 years of age. Although mumps virus infection is contagious, it is less communicable than measles and varicella. The degree of communicability is estimated most accurately by serologic surveys of exposed individuals because as many as one fourth of the infections with mumps virus occur without clinical symptoms.

Isolation of the patient within the hospital setting or in homes, when it is attempted, has not effectively curtailed spread of disease. This is usually attributed to the period of virus shedding that occurs prior to the symptomatic onset of illness and thus precedes the recognition of infection. As previously mentioned, one fourth of patients have an asymptomatic infection, but they also excrete virus. Their infection is self-limited, and their immunity is comparable to those with symptomatic infection. To the best of our knowledge, there are no animal reservoirs or human carriers of mumps virus.

Diagnostic Approach

The work of Johnson and Goodpasture first established that mumps was caused by a filterable virus and demonstrated that rhesus monkeys could be experimentally infected. The description of the complement-fixation test and successful propagation of virus in chick embryo preceded the now generally employed standard tissue culture techniques. These methods employ monolayers of one of several cell types, including primary monkey kidney, human amnion, or human kidney and cell lines, such as HeLa. In vitro multinucleate giant cells are seen, and hemabsorption inhibition provides a practical means of identification of the virus. With these techniques, virus has been isolated from such varied sources as blood, cerebrospinal fluid, urine, saliva, salivary gland tissue, and human milk.

In many academic and large hospital settings, viral diagnostic laboratories are available, and virus isolation can be attempted from clinical materials. The responsible laboratory will provide directions for submitting materials for culture. Saliva and urine can be collected at the time of clinical central nervous system symptoms and submitted for culture. Mumps isolation in tissue culture is usually not necessary for either diagnosis or management of patients with parotitis, but the techniques and facilities are available for defining the unusual or complicated situation.

For practical reasons, many diagnostic laboratories offer more extensive serologic diagnosis than cultural facilities for virus isolation. They will evaluate sera for the presence of antibodies to mumps virus. The serum for evaluation should be obtained as early as possible in the illness, and a convalescent specimen should be obtained after an interval of 2 to 3 weeks. A pair of sera can determine whether a specific illness is mumps infection by demonstrating an increase in antibody titer. A single serum can determine whether a person has ever had mumps infection but cannot define when it occurred. As indicated above, there are several types of antibody elicited by mumps infection.

Treatment

There is no specific therapy available for mumps infection. Symptomatic management of patients includes adequate hydration and analgesic and antipyretic therapy.

Prophylaxis and Immunization

The problem repeatedly occurs of what to do after exposure to mumps infection. Usually the person concerned is an adult without previous symptomatic mumps infection. Hyperimmune globulin or pooled serum IgG has been administered after exposure, with no proven efficacy. However, there has been a controlled study purporting to demonstrate that the administration of hyperimmune globulin after the appearance of parotitis can decrease the incidence and severity of orchitis. For this reason, hyperimmune globulin has been administered to postpubertal males who already have parotitis.

There has been limited experience in Scandinavia using a formalin-inactivated mumps vaccine, which affords some short-term protection from infection. No anti-F protein antibodies are demonstrable. It is probable that the F protein, which is sensitive to formalin, is not present. However, animal studies suggest that whole virus preparations can only induce anti-HN antibodies when the virus fails to replicate in the host. Purified F protein is an effective immunogen, and antibody to this protein is necessary to limit cell-to-cell spread of virus.

Live attenuated mumps virus vaccine was licensed in January 1968 and is available for prophylactic use. It is recommended for administration to children more than 1 year old and to young adults for induction of immunity parallel to that induced by natural infection. Vaccine should not be given to pregnant women because of the potential vulnerability of the fetus. Although no data exist that demonstrate transmission of attenuated virus to the fetus, placental infection has been documented after maternal immunization. For practical purposes there is only a single serologic strain of mumps virus, hence a single infection with either natural or attentuated virus confers immunity. The vaccine is a live attenuated virus produced in tissue cultures of chick embryo fibroblasts and is administered parenterally. Virus is not shed by the vaccinee, and immunization does not cause any side effects. The vaccine produces 95 to 100 percent serologic conversion from antibody-negative to antibody-positive in vaccinated susceptibles. The antibody levels, although considerably lower, parallel those produced by natural infection and persist for the 12 to 15 years that vaccine has been available for

HAPTER 75

ubella (German Measles)

linical Features and Pathogenesis
)idemiology
Diagnosis
Treatment and Prevention

the mid-19th century until 1941, rubella was regard- a benign childhood exanthem. When the Australian almologist, Sir Norman Gregg, reported the associa- f intrauterine rubella infection with congenital cata- this attitude changed completely. Subsequently, ss, congenital heart disease, and other malforma- were found to result from maternal rubella during st 4 months of pregnancy. The recovery in 1962 of virus in cell culture systems led to the development 1969, the licensure of attenuated active vaccines ve proven safe and effective. Congenital rubella has e infrequent in the United States as a result of wide- use of these vaccines.

the basis of its biochemical and biophysical prop- rubella is classified as a togavirus, but it has no in- ent with arthropod vectors. Because many different may cause a similar clinical illness with rash and fe- only rubella is teratogenic, virus isolation tech- and specific serologic tests for antibody have d the necessary differentiation of etiologic agents.

al Features and Pathogenesis

is a mild rash disease that occurs principally in but is seen at all ages. As shown in Figure 75-1, bation period is approximately 2 weeks, with mini- dromal signs or symptoms. Most often, the first ss of illness is mild fever and respiratory signs im- y preceding the onset of rash. The exanthem is ules and papules, at first on the face and then on k, trunk, and extremities, where they remain and rarely coalesce. The rash has ordinarily disap- y the third day. Preceding and accompanying the re is lymphadenopathy, which may involve the ular, suboccipital, and cervical nodes. Rash is observed commonly among children, but infection may be occult or only a febrile pharyngitis in as many as one third of adult patients. Although major complications are rare (thrombocytopenic purpura and encephalitis), the incidence of arthralgia and arthritis is much greater than generally appreciated. The frequency of joint involvement is directly correlated with increasing age and appears also to be more common among women. In a few patients, persistence of rubella virus in synovial cells has been associated with polyarthritis and arthralgia of lengthy duration. Usually joint involvement is acute and transient without sequelae (Fig. 75-1).

The route of infection is via the respiratory tract, with spread to lymphatic tissues and then to the blood. Both viremia and respiratory tract shedding of virus may precede the rash by 1 week, and the latter may follow it for another several weeks. Because much virus excretion occurs prior to the recognition of illness, secondary infection of intimate contacts has usually transpired before the primary patient has been diagnosed. Little is known of the actual pathology of the postnatal disease because it is not a fatal one. However, the pathogenesis of congenital infection has been well studied during and since the 1964 pandemic. Maternal viremia is followed by infection of the placenta, which may lead to virus invasion of the fetus. Multiple tissues and organs support the replication of virus, which continues to multiply throughout the remainder of pregnancy and in the postnatal period. A large percentage of maternal infections that occur in the first 3 months of pregnancy result in fetal illness. There is a diminishing number in the fourth month, and it is uncertain whether any fetal infections have resulted from maternal rubella in later pregnancy. Although the exact mechanism of damage to fetal organs is not clear, rubella infection of human embryonic cells in vitro is associated with both chromosomal breakage and inhibition of normal mitosis. Infants with